“First Experience with a Novel Inhibitor of Vascular Calcification (SNF472) in Healthy Volunteers and ESRD Patients on Hemodialysis”

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Introduction to SNF472

- **IP6**: myo-inositol hexaphosphate (MW = 792 Da)
- **IP6**: potent modulator of calcification
- Natural nutritional ingredient, **GRAS listed**
- **Low oral availability** (highly polar)
- **SNF472**: modified IP6 salt, i.v. formulation
- IP6 found in blood and intracellular compartment.
- Physiological levels: blood < 0.3 uM / Intracellular 10-100 uM
- **SNF472** impacts on **extracellular** compartment levels
- Expected **therapeutic** concentrations 2-3 uM
- **SNF472** in clinical development for cardiovascular calcification in ESRD dialysis patients and calciphylaxis
The relevance of cardiovascular calcification

- Progression of CACs predicts CV events and all-cause mortality

**General Population**

- Budoff et al J Am Coll Cardiol 2010

**CKD2-5**

- Russo et al Kidney Int 2011

**CKD5-ESRD**

- Bellasi 2012, oral communication
The mechanism of CVC involves the interaction of calcium, phosphate, and various factors.

**SNF472** directly inhibits the final common step.

### Repressors
- MGP
- OPN
- Fetuin
- Pyrophosphate
- Vit K

### Promoters
- Vit D
- FGF23
- Inflammatory cytokines
- Lipids
- Apoptotic bodies
- Necrotic debris
- Nucleational complexes

#### Risk Factors
- Calcium x Phosphate > 55
- Calcium > 10.8 / Phosphate > 5.5 mg/dl

### Mechanism
- SNF472 targets the vascular calcification process by inhibiting the final common step.
SNF472. Mechanism of Action

**Physico-chemical MoA:** prevents cardiovascular calcification (CVC) by blocking Ca-crystal formation/growth

- **Soluble ions in biological fluids**
- **Calcium**
- **Phosphate**
- **Water**

- **Nucleation**
- **Crystal growth**
  - Hydroxyapatite: $Ca_{10}(PO_4)_6(OH)_2$
1) Study in 16 male healthy volunteers (HV)
Single ascending dose (SAD), 2 cohorts

2) Study in 8 male haemodialysis patients (HD)
Single dose
Results: PK data

[Graph showing PK data with different doses (5 mg/kg, 9 mg/kg, 12.5 mg/kg) and estimated therapeutic levels over time (0 to 8 hours).]
Results: PK data

[Graph showing PK data for different doses of SNF472 with error bars indicating variability.]

- 5 mg/kg HV
- 9 mg/kg HV
- 12.5 mg/kg HV

Estimated Therapeutic Levels

9 mg/kg HD patients *

* Provisional data
## Results: Safety data

No SAEs / blind not broken / stopping criteria not met

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>i.v. Conc. (mg/ml)</th>
<th>Plasma levels Cmax (ng/mL)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>0.8</td>
<td>&lt; 500</td>
<td>2/6</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>11 500</td>
<td>5/6</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
<td>22 400</td>
<td>3/6</td>
</tr>
<tr>
<td>12.5</td>
<td>1</td>
<td>40 250</td>
<td>4/5</td>
</tr>
<tr>
<td><strong>HD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>17 500</td>
<td>No effects</td>
</tr>
</tbody>
</table>
Results in HV: effect on Ca^{2+}

- No clinical signs of hypocalcemia
- No ECGs abnormalities
- In HD patients ionized calcium levels were stable
Pharmacodynamic measurements

Measures blood calcification propensity ex-vivo
Estimates the effect of drugs on calcification potential

80 µl plasma

0.15 M NaCl, pH 7.40
+ 12.5 mM Ca\(^{2+}\)
+ 1.5 mM HPO\(_4\)^{2-}\)

30 minutes
750 r.p.m.
Room temperature

Light scattering
Reading at 550 nm
Every 3 minutes
Pharmacodynamic measurements

- Test responds (D-R) to inhibition potential, independently of inhibitor’s MoA
- Allows to compare crystallization potential between samples
- Allows to compare crystallization inhibitor potency and efficacy

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Efficacy (%)</th>
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<tbody>
<tr>
<td>SNF472</td>
<td>100</td>
</tr>
<tr>
<td>Pyrophosphate</td>
<td>80</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>60</td>
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<tr>
<td>Pamidronate</td>
<td>40</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
<td>20</td>
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<tr>
<td>Citrate</td>
<td>0</td>
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<tr>
<td>Fetuin</td>
<td>-20</td>
</tr>
</tbody>
</table>

Efficacy (%) vs. [Inhibitor] (µM)
PK-PD in non-clinical models

- 12-day rat model, VitD induced calcification
- 4 groups: placebo and 3 dose levels of i.v. SNF472 (3, 10, 30 mg/kg)
Results phase 1: PD data in HD
Conclusions

- First-in-human trial with SNF472 in HV and HD patients
- SNF472 novel mechanism of action, physico-chemical
- Good safety and tolerability
- Adequate PK profile, suggesting low SNF472 clearance through the dialysis membrane
- SNF472 reduces vascular calcification in animal models and calcification propensity in HD patients at 9 mg/kg
- Data supports continuation of the clinical program in CUA and ESRD dialysis patients
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